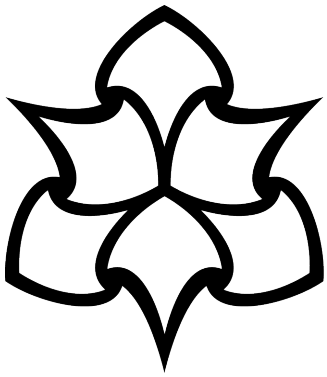

Hydrogel Drug Delivery: Diffusion Models

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1 Introduction

The delivery of drugs for pharmaceutical and medical applications is usually achieved through a variety of drug delivery systems such as injections, tablets and sprays. These systems must deliver the correct dose of the drug in an efficient manner, that is: a controlled delivery which maintains the optimal concentration within the bloodstream in order to be therapeutically effective for reasonable periods of time [13]. Typically, such delivery systems produce an initial rise of drug concentration reaching a peak after which it falls off so that another dose is required to maintain drug effectiveness. At times this concentration may rise above the maximum therapeutic range, into the possibly toxic, while at others it falls below the minimum therapeutic level making the drug ineffective.
The ability to release the drug at therapeutically effective levels and maintain these levels for longer periods of time while avoiding such oscillatory behaviour is one of the objectives of a controlled release system. This allows the drug to be administered in a single dose while reducing the possibility of side effects. This requires the design of new systems with an understanding of their release behaviour while optimising their release kinetics [11].
The majority of controlled release devices consist of drugs dispersed within a polymeric carrier, commonly hydrogels.

1.1 Hydrogels

Hydrogels are three-dimensional, water-swollen structures mainly composed of hydrophilic polymeric networks containing chemical or physical cross-links [12]. Hydrogels can imbibe water or other biofluids with some being able to swell to ten times

their original volume. Hydrogels have been used for medical applications for some time. Upon absorption of water a hydrogel changes from its often dry non-swollen state to a gel-like state which exhibits rubbery behaviour with an ability to resemble bodily tissues therefore possessing good biocompatibility [12]. The medical applications of hydrogels inlude: the use of PHEMA (poly-2-hydroxyethyl methacrylate) for soft contact lenses, PVA (poly-vinyl-alcohol) in artificial cartilage and Cellulose acetate for artificial kidneys as well as for biosensors, sutures and dental materials [14]. However, it is their ability to act as drug release devices which is the focus of this report.

1.2 Drug Release Systems

Drugs may be enclosed or immersed within a hydrogel and correspond to several different types of controlled release systems: diffusion-controlled systems, swelling controlled systems, chemically controlled systems and environmentally responsive systems [14]. We are mainly interested in diffusion and swelling-controlled systems.

1.2.1 Diffusion-Controlled Release Systems

There are two types of diffusion controlled release systems: reservoir devices and matrix devices. In each case the release of the drug occurs by diffusion through the hydrogel mesh or the water-filled pores.

1. Reservoir Systems: a reservoir delivery system consists of a drug core enclosed in a hydrogel membrane, usually in the form of capsules, cylinders, spheres or slabs. In order to maintain a constant release rate the drug concentration difference must remain constant. This is achieved by concentrating the drug in the centre of the device. The drug release behaviour of the device is shown in Figure 1.

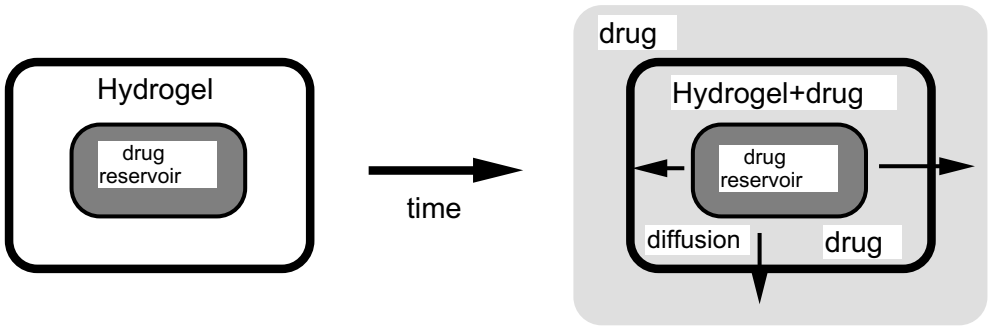


Figure 1: Drug release from a reservoir system by diffusion through the hydrogel membrane.

2. Matrix Systems: in matrix systems the drug is dispersed throughout the hydrogel lying within the three-dimensional structure of the polymer. Matrix tablets are constructed through a compression of a mixture of drug and polymer powders. Drug release occurs through the macromolecular mesh or water-filled pores. Note that the release rate is here proportional to the square root of time initially rather than the constant time-independent rate available with reservoir systems. The drug release characteristics of matrix devices is shown in Figure 2.

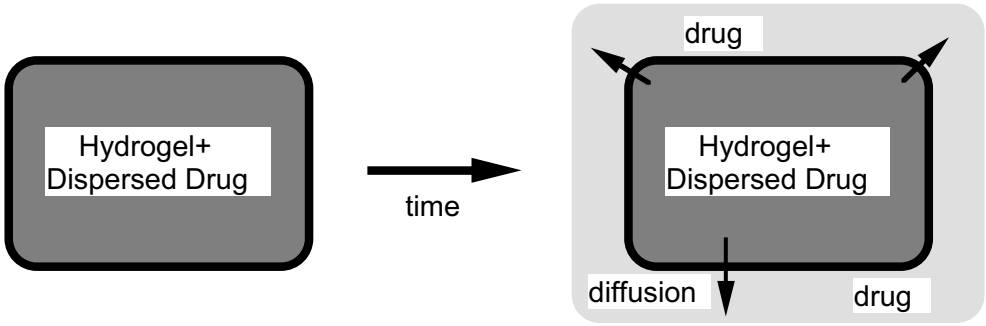


Figure 2: Drug release from a matrix system by diffusion through the entire hydrogel.

1.2.2 Swelling-Controlled Release Systems

In swelling-controlled release systems the drug is dispersed within a glassy polymer as in a matrix device. Once the polymer comes into contact with water or another

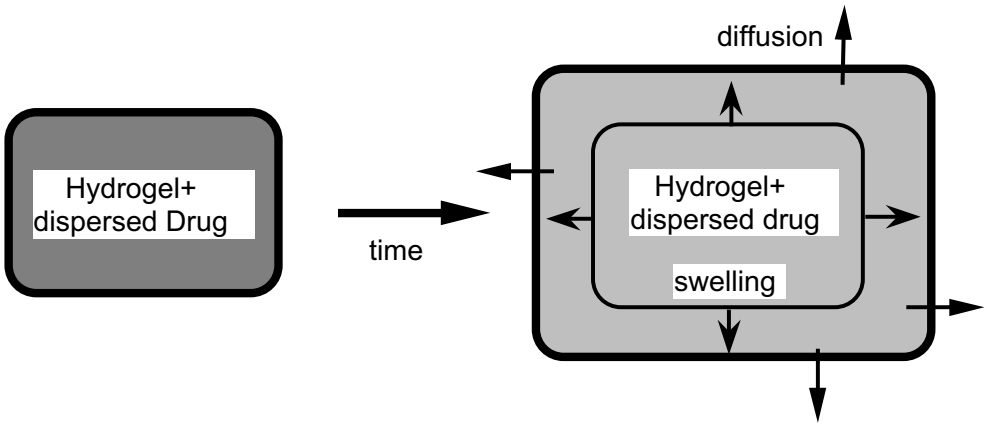


Figure 3: .

biofluid it begins to swell. The glass transition temperature of the polymer is lowered

allowing a relaxation of molecular chains so that the drug can now diffuse out of the swollen rubbery area of the polymer [14]. Figure 3 shows how the swelling edge of the tablet expands beyond its original boundary. This is also known as Case II transport and is characterised by constant, i.e. time-independent, release kinetics. In some cases a combination of swelling controlled release as well as diffusion occurs, this is known as anomalous transport [13].

2 Diffusion in Hydrogels

Once a matrix delivery device comes in contact with a surrounding biofluid a concentration gradient will exist between the dispersed drug within the hydrogel and the ambient fluid. The transport of drug is now possible from a high concentration through the hydrogel into the surrounding fluid, at a lower concentration [15]. The flux of drug, $\mathbf{J}$, is proportional to the driving force, ∇c (concentration gradient) as:

$$\mathbf{J} = -D\nabla c$$

where D, the diffusion coefficient of the drug in the polymer, cm^2/s, c is the concentration of the drug in the polymer, $\mathrm{mol}/\mathrm{cm}^3$, and J is the molar flux of the drug in $\mathrm{mol}/\mathrm{cm}^2\mathrm{s}$. Usually the release rate is time dependent so that the release behaviour is determined from the unsteady diffusion problem:

$$\frac{\partial c}{\partial t} = -\nabla \cdot \mathbf{J} = \nabla \cdot (D\nabla c) \tag{1}$$

with associated boundary and initial conditions. Note that here the diffusion coefficient may be space dependent. This equation represents the one-dimensional transport of drug with non-moving boundaries.
Typically, the problem considered is the diffusion of drug out of the hydrogel, possessing a high concentration, into the surrounding fluid, possessing a low concentration. For simplicity the initial concentration inside the hydrogel is given as unity throughout whereas the concentration in the ambient fluid is assumed to be zero. The boundary conditions at the hydrogel boundary remain zero, these are so-called perfect sink conditions such that the drug is immediately carried away into the fluid so that a concentration gradient always exists at the interface between the hydrogel and the ambient fluid. This is summarised in Figure 4.

2.1 Drug Release from Hydrogels

Equation (1) is a diffusion equation with a non-moving boundary. That is, the hydrogel is not swelling. It describes the diffusion of drug out of the hydrogel while the boundary is static, this will be known as *Static Drug Delivery*. On the other

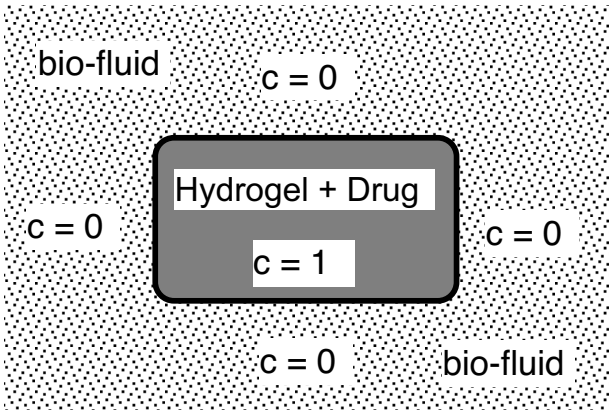


Figure 4: Initial conditions in the hydrogel/biofluid system showing sink conditions at and beyond the hydrogel/fluid boundary.

hand when the hydrogel is undergoing swelling the process will be called *Dynamic Drug Delivery*.

2.1.1 Static Drug Delivery

The solution of the diffusion equation (1) may be carried out in several ways using either Laplace transforms or separation of variables, especially in the simple case of constant diffusion coefficient, $\nabla D \equiv 0$. The information obtained from these solutions includes [12]:

1. drug concentration profiles in the polymer during release which are obtained directly from the solution of equation (1).

2. the amount or mass of drug released M_t which may be normalised with respect to the amount released at infinite time M_∞, i.e. the fractional release of the drug, M_t/M_∞.

Peppas [1] has shown that, for diffusion with a constant diffusion coefficient and perfect sink conditions, the fractional drug release for short times is given by:

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

for k a constant and the diffusional exponent n is 0.5. This is confirmed by experimental results which distinctly show drug release behaviour that is linear with $\sqrt{t}$, at least initially.

2.1.2 Dynamic Drug Delivery

It is well known that hydrogels will swell upon contact with water. The process of diffusion out of the polymer while this is occurring has not yet been fully researched and remains an ongoing research topic. Experimental results have also shown that the drug release behaviour from a swelling polymer is different from that of a non-swelling one. It may undergo both Case II and anomalous transport which is demonstrated by time-independent, zero order release kinetics, or time-dependent release behaviour with a diffusional exponent between 0.5 and 1, respectively.
Although the consequences of swelling behaviour have been demonstrated experimentally little theoretical work has investigated this process. One aspect of the swelling behaviour of hydrogels is how the diffusion characteristics change as the boundary of the original hydrogel grows. In addition, it is known that the diffusion coefficient may be dependent on the degree of swelling [15, 11]. If the degree of swelling can be measured by the convective velocity of the moving boundary it becomes time dependent. These two aspects of diffusion from swelling hydrogels is the reason for the current investigation.

2.2 Aims of the Current Study

This report is concerned with controlled-release systems of the matrix type. Given the possibility of catastrophic failure of reservoir systems and the sudden release of the entire drug contents into the body, matrix systems are prefered. As noted above matrix systems are usually drug delivery devices which use a hydrogel as the carrier of the dispersed drug. Hydrogels will swell upon contact with water or other biofluids so that a model describing swelling behaviour in conjunction with diffusion is necessary. As well, the diffusion coefficient may become time-dependent which requires further study.
The aims of the current study are to derive and analyse a model for hydrogel drug delivery devices which include:

1. Diffusion processes in a swelling hydrogel.

2. The variation of the diffusion coefficient with the degree of swelling.

3 Drug Diffusion in a Swelling Hydrogel

The release of drugs for medical applications is often carried out by encapsulating the drug within a polymer which may swell upon absorption of fluid. Define the concentration of the drug within the polymer, at any time in a three dimensional domain, as $c = c(x, y, z, t)$. The drug diffuses out of the domain at the boundaries

which may themselves swell or grow as water/fluids are absorbed. The general advection-diffusion equation for a growing domain is given by [8]:

$$\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) - \nabla \cdot (c\mathbf{u})$$

which becomes, for a constant diffusion coefficient, $\nabla D \equiv \mathbf{0}$:

$$\frac{\partial c}{\partial t} = D\nabla^2 c - \nabla \cdot (c\mathbf{u})$$

In only one dimension, $\mathbf{u} = u\mathbf{i}$ this reads:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - u\frac{\partial c}{\partial x} - \frac{\partial u}{\partial x}c$$

The term on the left expresses the local rate of change of concentration over time, whereas the three terms on the right hand side express the advection of elemental volumes moving with the flow i.e. uc_x, the dilution term $u_x c$ is due to local volume change and the first term expresses the diffusion of the concentration.
Typically, such release occurs via the diffusion of the drug from within the polymer through the boundary. For simplicity the initial drug concentration is assumed to be unity in the whole domain, $0 < x < X(0)$. The concentration at the growing boundary $x = X(t) = Lf(t)$ (where $f(t) > 1$ for all time) at any time is assumed zero, here making use of sink conditions. The problem is symmetric about the boundaries and can then be expressed as :

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - c\frac{\partial u}{\partial x} - u\frac{\partial c}{\partial x} \qquad \text{in } 0 < x < X(t),\ t > 0 \tag{3}$$

subject to:

$$\begin{array}{ll} c(x,0) = 1 & 0 < x < X(0) \\ X(0) = L & \\ \left.\begin{array}{l} \frac{\partial c}{\partial x}(0,t) = 0 \\ c(X(t),t) = 0 \end{array}\right\} & \text{for } t > 0 \end{array} \tag{4}$$

The initial condition is shown in Figure 5.

3.1 Uniform Growth Velocity in $0 \leq x \leq X(t)$

At time $t = 0$ two facts are known: (i) the velocity at the left edge of the domain $u(0,0) = 0$ and (ii) that of the right edge $u(X(0),0) = \dot{X}(0) \neq 0$. For $t > 0$ the left edge velocity remains clamped at zero whereas the right edge grows i.e.

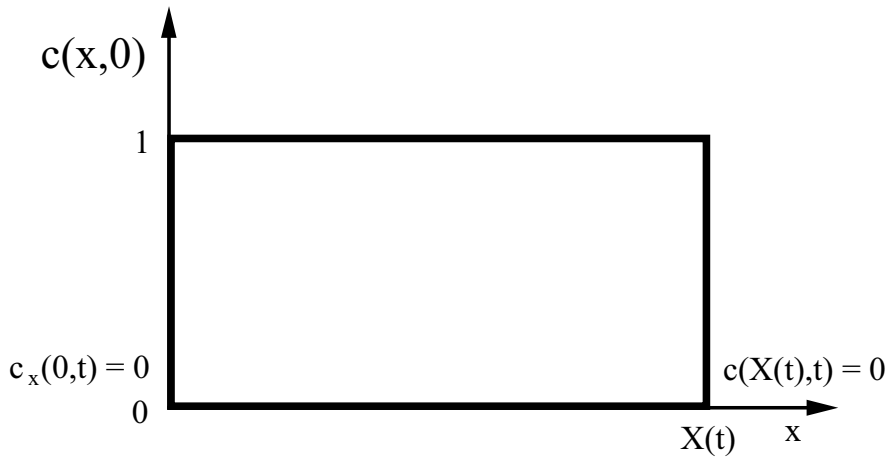


Figure 5: The initial concentration $c(x,0) = 1$, in $0 < x < X(t)$ with boundary conditions $\partial c(0,t)/\partial x = 0$ and $c(X(t),t) = 0$ for $t > 0$.

$u(X(t),t) = \dot{X}(t)$. A velocity gradient must exist across the domain. Therefore we may immediately say that:

$$u(X(t),t) - u(0,t) = \int_0^{X(t)} \frac{\partial u}{\partial x}\, dx$$

or:

$$\frac{dX}{dt} = \int_0^{X(t)} \frac{\partial u}{\partial x}\, dx$$

We adopt the simple model of uniform growth, see [9, 10, 5], i.e. $\partial u/\partial x$ is independent of x and only a function of t, or $\partial u/\partial x = \sigma(t)$, we have:

$$\dot{X}(t) = \sigma(t) \int_0^{X(t)} dx = X(t)\sigma(t) \Rightarrow \sigma(t) = \frac{\dot{X}}{X}$$

therefore:

$$\frac{\partial u}{\partial x} = \frac{\dot{X}}{X}, \quad \text{and} \quad u(x,t) = \frac{\dot{X}}{X} x$$

3.1.1 Final Advection-Diffusion Equation

The PDE (3) becomes:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - \left(\frac{\dot{X}}{X}x\right)\frac{\partial c}{\partial x} - \left(\frac{\dot{X}}{X}\right)c \qquad \text{in } 0 < x < X(t),\ t > 0 \tag{5}$$

$$\left.\begin{array}{ll} c(x,0) = 1 & 0 < x < X(0) \\ X(0) = L & \\ \frac{\partial c}{\partial x}(0,t) = 0 & \\ c(X(t),t) = 0 & \end{array}\right\} \quad \text{for } t > 0 \tag{6}$$

3.1.2 The Landau Transformation

The convective term may be removed by use of the Landau transformation [7], so that the system (5), (6) is now, see Appendix 6.1

$$\frac{\partial c}{\partial \tau} = \frac{D}{X^2}\frac{\partial^2 c}{\partial \zeta^2} - \frac{\dot{X}}{X}c \qquad \text{in } 0 < \zeta < 1,\ \tau > 0 \tag{7}$$

$$\begin{gathered} c(\zeta, 0) = 1 \qquad 0 < \zeta < 1 \\ \left.\begin{array}{l} \frac{\partial c}{\partial \zeta}(0, \tau) = 0 \\ c(1, \tau) = 0 \end{array}\right\} \quad \text{for } \tau > 0 \end{gathered} \tag{8}$$

this is the one dimensional advection-diffusion equation in a growing domain.

3.2 Concentration and Drug Release Profiles

3.2.1 Solution in Terms of Trigonometric Functions

The solution may be obtained by separation of variables, see Appendix 6.2, giving

$$c(\zeta, \tau) = \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)}\frac{L}{X(\tau)}\cos\left(\frac{(2n+1)\pi\zeta}{2}\right)e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_0^\tau X^{-2}\,dt} \tag{9}$$

or in terms of the original variables:

$$c(x, t) = \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)}\frac{L}{X(t)}\cos\left(\frac{(2n+1)\pi x}{2X(t)}\right)e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_0^t X(t')^{-2}\,dt'}$$

3.2.2 Fractional Drug Release

Now define the fractional drug release in terms of the original variables as:

$$M(\tau) = 1 - \frac{\int_0^{X(\tau)} c(x, \tau)\,dx}{\int_0^{X(0)} c(x, 0)\,dx}$$

which relates the ratio of the total mass in the volume $X(\tau)$ to the initial mass in volume L. This ratio must decrease as the volume increases. In terms of the new variables ζ and τ:

$$\begin{aligned} M(\tau) &= 1 - \frac{\int_0^1 c(\zeta, \tau)X(\tau)\,d\zeta}{\int_0^1 c(\zeta, 0)X(0)\,d\zeta} \\ &= 1 - \frac{X(\tau)}{L}\int_0^1 c(\zeta, \tau)\,d\zeta \end{aligned}$$

therefore inserting the solution (9) we have:

$$M(\tau) = 1 - \frac{X}{L}\int_0^1 \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)}\frac{L}{X}\cos\left(\frac{(2n+1)\pi\zeta}{2}\right)e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_0^\tau X^{-2}\,dt}\,d\zeta$$

$$= 1 - \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)}e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_0^\tau X^{-2}\,dt}\int_0^1\cos\left(\frac{(2n+1)\pi\zeta}{2}\right)\,d\zeta$$

so that:

$$M(\tau) = 1 - \sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_0^\tau X^{-2}\,dt} \tag{10}$$

again, in terms of the original variables we have:

$$M(t) = 1 - \sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_0^t X(t')^{-2}\,dt'}$$

note that the fractional drug release always depends on the flux on the outer boundary at $\zeta = 1$, see Appendix 6.3. This also means that if the flux condition at $\zeta = 1$ is zero, $c_\zeta(1,\tau) = 0$, then so is the fractional drug release for all time.

4 Static and Dynamic Drug Release

Define the case where the domain is stationary as the static case, i.e. $\dot{X} = L\dot{f} = 0$, then

$$M_S(\tau) = -\frac{D}{L^2}\int_0^\tau c_\zeta(1,t)\,dt$$

and the dynamic case where $\dot{X} = L\dot{f} \neq 0$:

$$M_D(\tau) = -\frac{D}{L^2}\int_0^\tau \frac{c_\zeta(1,t)}{f(t)}\,dt$$

This implies that:

$$M_D(\tau) - M_S(\tau) = -\frac{D}{L^2}\int_0^\tau\left(1 - \frac{1}{f(t)}\right)|c_\zeta(1,t)|\,dt$$

since the flux at the outer boundary $\zeta = 1$ is always negative. And for $f(t) > 1$ for all t the term $1 - 1/f > 0$ so that this integral is always positive which implies that the difference between the dynamic and static drug release is always negative, i.e. in terms of original variables

$$M_D(t) < M_S(t)$$

for all time. This means that the dynamic drug release is never as much as the static release.

4.1 Static Drug Release: $\dot{X} = 0$

For the case of a stationary boundary, i.e. a non growing boundary having $X(\tau) = L$ for all time the solution (25) becomes:

$$c(\zeta, \tau) = \frac{4}{\pi} \sum_{n=0}^{\infty} \frac{(-1)^n}{(2n+1)} \cos\left(\frac{(2n+1)\pi\zeta}{2}\right) e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 \tau}$$

with an associated fractional drug release as (in terms of t)

$$M_S(t) = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 t} \tag{11}$$

4.1.1 Fractional Drug Release for Short Times

The above solution for the stationary boundary case (11) may be rewritten in terms of complimentary error functions:

$$M_S(t) = 2\sqrt{\frac{Dt}{L^2}} \left[\frac{1}{\sqrt{\pi}} + 2\sum_{n=1}^{\infty} (-1)^n \text{ierfc}\left(\frac{nL}{\sqrt{Dt}}\right)\right] \tag{12}$$

Note that by definition [2]:

$$\text{ierfc } x = \frac{e^{-x^2}}{\sqrt{\pi}} - x\text{erfc } x$$

so that for large x, erfc $x \to 0$, $e^{-x^2} \to 0$ and so ierfc $x \to 0$. Therefore

$$\lim_{t \to 0} \text{ierfc}\left(\frac{nL}{\sqrt{Dt}}\right) = 0$$

so that for t small

$$M_S(t) \simeq 2\sqrt{\frac{Dt}{L^2}} \frac{1}{\sqrt{\pi}} = kt^{\frac{1}{2}} \tag{13}$$

where $k = (2/L)\sqrt{D/\pi}$. Reproducing the solution (2) obtained in [1].

4.1.2 The Characteristics of Fractional Drug Release

The graphs of Figure 6 show fractional drug release $M(\tau)$ a function of (a) τ and (b) $\tau^{1/2}$. Clearly for small times studied $\tau : 0 \to 0.25$ s the fractional drug release is directly proportional to the square root of time.

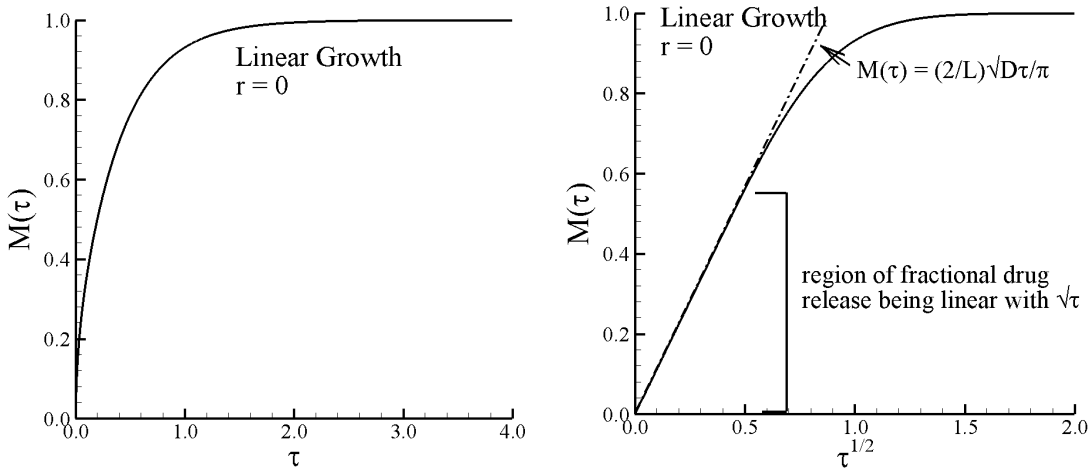


Figure 6: Fractional drug release $M(\tau)$ as a function of (a) τ and (b) $\sqrt{\tau}$ for the static case with $L = D = 1$.

4.1.3 Fractional Drug Release: Comparison over Longer Times

Consider now how the solution for small times (13), i.e.

$$M_S(\tau) = \frac{2}{L}\sqrt{\frac{D}{\pi}}\tau^{1/2}$$

compares to the analytical (12) solution for longer times. Figure 7 shows how the

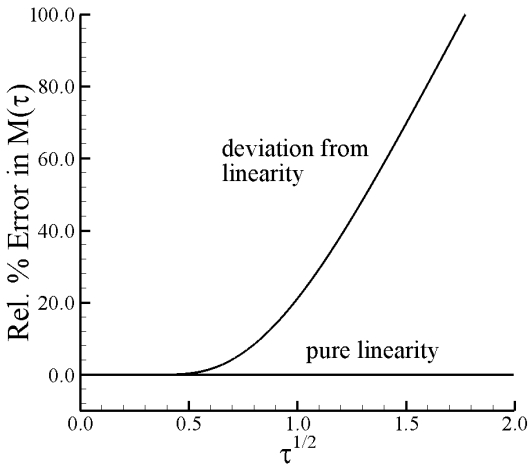


Figure 7: Deviation of the fractional drug release small time solution compared with the solution for longer times as a function of $\tau^{1/2}$.

small time solution compares to the analytical solution over longer times. Figure 6(b) indicates that the small time solution starts to deviate from the long time case beyond about $\tau^{1/2} = 0.5$. This is confirmed in Figure 7 where the relative difference between the analytical solution and the small time solution also starts to vary at around $\tau^{1/2} = 0.5$. Here we have used:

$$\text{Rel. \% Diff} = \left| \frac{M_S(\tau) - 2\sqrt{D\tau/\pi L^2}}{M_S(\tau)} \right| \times 100$$

4.2 Dynamic Drug Release: $\dot{X} \neq 0$

We may choose various possible growth functions for $X(\tau)$. Typical choices include linear growth, exponential growth and logistic growth, see Landman *et al* [9]. The first two: linear and exponential growth are ever growing domains which tend to an infinite volume as time increases; the third, logistic growth, expands the volume only to a multiple of the original length mL. Whereas the r parameter acts as a growth factor, expressing how fast the volume grows in the first two cases, the third case r is a parameter which speeds up or slows down the expansion towards the final volume mL.

4.2.1 Linear Growth

This represents a function of the form

$$X(\tau) = L(1 + r\tau), \qquad \dot{X} = Lr$$

where r is the growth factor. The integral

$$\int_0^\tau X(t)^{-2}\, dt = \frac{\tau}{L^2(1 + r\tau)}$$

the fractional drug release is

$$M_D(\tau) = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2\left(\frac{\tau}{1+r\tau}\right)} \tag{14}$$

Note that as $\tau \to \infty$ the mass of drug released attains a constant value given by:

$$M_{rel} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} e^{-\frac{D}{r}\left(\frac{(2n+1)\pi}{2L}\right)^2} \tag{15}$$

4.2.2 Exponential Growth

This represents a function of the form:

$$X(\tau) = Le^{r\tau}, \qquad \dot{X} = Lre^{r\tau}$$

The integral

$$\int_0^\tau X(t)^{-2}\, dt = \frac{1}{2rL^2}(1 - e^{-2r\tau})$$

the fractional drug release is

$$M_D(\tau) = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2\left(\frac{(1-e^{-2r\tau})}{2r}\right)} \tag{16}$$

The mass of drug released reaches a constant value as time increases given by:

$$M_{rel} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} e^{-\frac{D}{2r}\left(\frac{(2n+1)\pi}{2L}\right)^2} \tag{17}$$

4.2.3 Logistic Growth

This represents a function of the form:

$$X(\tau) = \frac{Le^{r\tau}}{1 + (1/m)(e^{r\tau} - 1)}, \qquad \dot{X} = \frac{Lre^{r\tau}(1 - 1/m)}{\left[1 + (1/m)(e^{r\tau} - 1)\right]^2}$$

where m is the ratio of final to initial lengths. The integral

$$\int_0^\tau X(t)^{-2}\, dt = \frac{1}{2L^2m^2r}\left[(m-1)^2(1 - e^{-2r\tau}) + 4(m-1)(1 - e^{-r\tau}) + 2r\tau\right]$$

so that the fractional drug release reads:

$$M_D(\tau) = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} e^{-\frac{D}{2r}\left(\frac{(2n+1)\pi}{2mL}\right)^2\left[(m-1)^2(1-e^{-2r\tau})+4(m-1)(1-e^{-r\tau})+2r\tau\right]} \tag{18}$$

In this case for large times the mass of drug released looks like:

$$M_{rel} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} e^{-\frac{D}{2r}\left(\frac{(2n+1)\pi}{2mL}\right)^2\left[(m-1)^2+4(m-1)+2r\tau\right]}$$

$$= 1 - \sum_{n=0}^{\infty} \frac{8e^{-\frac{D}{2r}\left(\frac{(2n+1)\pi}{2mL}\right)^2[(m-1)^2+4(m-1)]}}{(2n+1)^2\pi^2} e^{-D\left(\frac{(2n+1)\pi}{2mL}\right)^2\tau}$$

4.2.4 Results : The Growing Boundary

For the case where the boundary is growing and this growth function is given beforehand, the solution may be found analytically, involving the evaluation of an integral in equation (10). We study two types of growth functions here: (i) growth functions which increase indefinitely and (ii) growth functions which increase up to a certain size but no further. The second of these is the more realistic and more correctly represents the swelling of the polymer. The swelling is assumed at first to be rapid and then gradually ebbing away to a given multiple of the initial volume. The characteristic case is logistic growth. Domain growth is shown in Figure 8 for

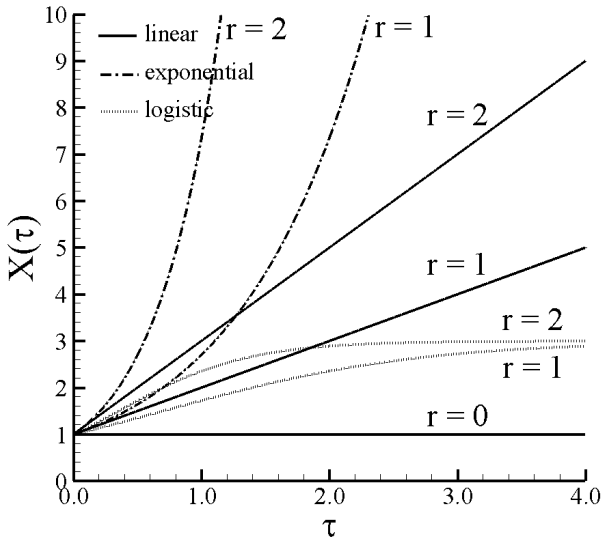
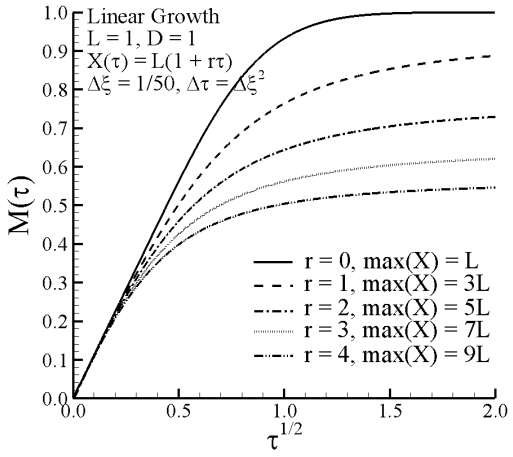


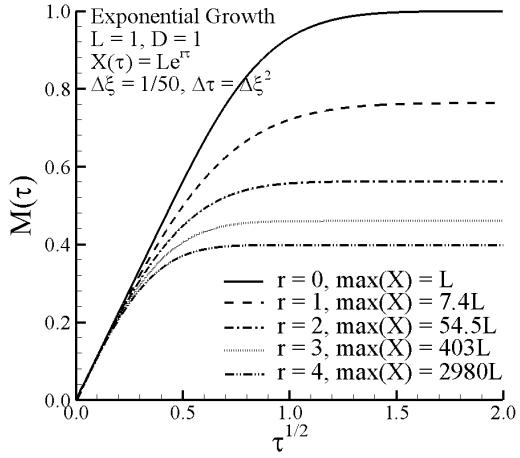
Figure 8: Growth functions of the indefinite type: linear (solid), exponential (dot-dash) and the finite type: logistic (dotted) for growth factors from $r = 0$ to $r = 2$.

both the two indefinite types: linear and exponential and the finite type: logistic for three values of growth factor $r = 0 \rightarrow 2$ and $m = 3$ for the logistic case. The $r = 0$ case is the same for each growth function type. Note that for the two indefinite types the growth factor r represents how fast the volume increases over time with the exponential case increasing at a much faster rate than the linear, see Figure 8 (dot-dash and solid lines). For the finite type, the logistic case, the parameter r represents how quickly the volume increases towards its final size which is expressed by the ratio of final to initial volume m, see Figure 8 (dotted line). The larger the value of r the faster the final volume is reached.
Typical results for the fractional drug release $M(\tau)$ over time is shown in Figure 9 for the linear, Figure 9(a), exponential, Figure 9(b) and logistic, Figure 9(c) cases. For each case we chose a space step of $\Delta\zeta = 1/50$ and time step of $\Delta\tau = 1/50^2$ with

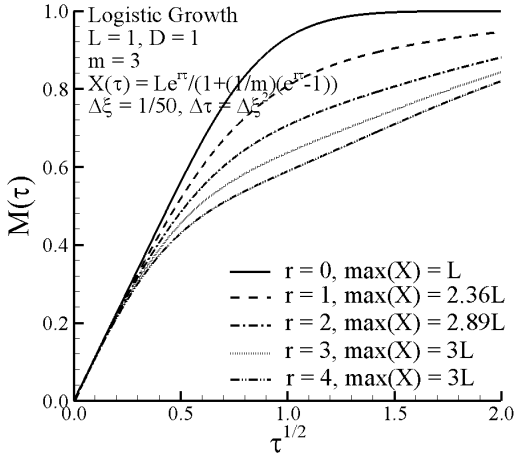
an initial length $L = 1$ and diffusion coefficient $D = 1$. Each graph indicates the maximum volume, as a multiple of L, reached for each value of r used.



(a) Linear Growth



(b) Exponential Growth



(c) Logistic Growth

Figure 9: Fractional drug Release $M(\tau)$ over time as a function of (a) linear, (b) exponential and (c) logistic growth for various values of the growth factor r and $m = 3$; with initial length $L = 1$, diffusion coefficient $D = 1$ for a grid of space step size $\Delta\zeta = 1/50$ and time step $\Delta\tau = 1/50^2$.

4.2.5 Linear Drug Release

Typically, the $r = 0$ case represents the diffusion of the drug out of the constant volume L over time. This remains linear in $\sqrt{\tau}$ until about $\sqrt{\tau} = 0.5$ after which the rate of drug release decreases until at around $\sqrt{\tau} = 1.5$ all of the drug has diffused

out (i.e. when $M(\tau) \simeq 1$). Compare this to the drug release as the volume increases. It is clear that for all cases where the volume increases with time (and $r > 0$) the drug release is less than for the constant volume case $r = 0$. In fact, over the times considered none of the $r > 0$ cases release all of the drug. It appears that as r increases less and less of the drug is released tending to a constant value of about $M(\tau) = 1/2$. From equation (27) we know that for long times:

$$M_D(\tau) = 1 - \frac{8}{\pi^2} \lim_{\tau \to \infty} e^{-\frac{D}{r}\left(\frac{\pi}{2L}\right)^2}$$

$$= 1 - \frac{8}{\pi^2} e^{-\frac{D}{r}\left(\frac{\pi}{2L}\right)^2}$$

so that for $L = D = 1$, $M_{rel} = 1 - \frac{8}{\pi^2} e^{-\frac{\pi^2}{4r}}$. The results are shown in Table 1. They agree well with those of Figure 9(a). This shows that in some cases where the boundary grows at a rapid rate not all of the drug is released from the polymer.

4.2.6 Exponential Drug Release

The aforesaid comments apply even more to the exponential case where all of the $r > 0$ cases release the drug at a much smaller rate than the $r = 0$ case and also at smaller rates than the linear case with the same growth factor r. Use of (27) for the exponential case implies

$$M_{rel} = 1 - \frac{8}{\pi^2} \lim_{\tau \to \infty} e^{-\frac{D}{2r}\left(\frac{\pi}{2L}\right)^2}$$

with $L = D = 1$:

$$M_{rel} \simeq 1 - \frac{8}{\pi^2} e^{-\frac{\pi^2}{8r}}$$

The results are shown in Table 1. This again agrees well with the results of Figure 9(b).

4.2.7 Logistic Drug Release

The logistic drug release behaviour is significantly different from that of the other two cases. This time the $r > 0$ cases all still release drug at a smaller rate than the $r = 0$ case but do not remain at near constant values for long periods of time. Instead there is a decrease in slope which then appears to become linear after a certain characteristic time. This time is smaller as r increases. It is also clear that in all of the logistic cases the drug is released more quickly than in the other cases with all of the various r cases converging to total drug release in a characteristic

	static	linear	exponential	logistic
r	M_{rel}	M_{rel}	M_{rel}	M_{rel}
0	1.00	1.00	1.00	1.00
1	NA	0.93	0.76	1.00
2	NA	0.76	0.64	1.00
3	NA	0.64	0.56	1.00
4	NA	0.56	0.40	1.00

Table 1: Table showing the amount of drug released for large times. Here, NA means Not Applicable.

time seemingly around $\sqrt{\tau} \simeq 2.5$.
Equation (27) shows that for $L = D = 1$ and $m = 3$:

$$M_{rel} \simeq 1 - \frac{8}{\pi^2} e^{-\frac{\pi^2}{36r}[6+r\tau]}$$

so that all the drug will eventually diffuse out. In fact it is easy to calculate that 99% of the mass will diffuse out by:

$$\tau_{99} = -\frac{6}{r} - \frac{36}{\pi^2} \ln\left(\frac{\pi^2}{\sqrt{800}}\right)$$

which gives:

$$\begin{aligned} r = 1: &\quad \tau_{99} \simeq 10 \\ r = 2: &\quad \tau_{99} \simeq 13 \\ r = 3: &\quad \tau_{99} \simeq 14 \\ r = 4: &\quad \tau_{99} \simeq 14.5 \end{aligned}$$

although by $\tau \simeq 2.5$, the $r = 1, 2, 3, 4$ cases have expended $M = 92, 82, 76, 73$ % respectively. Table 1 shows how much of the drug has been released over long times. The static case does not depend on r of course although the $r = 0$ case represents the static case and like the logistic case all of the drug has been released. In both the linear and exponential cases all of the drug is never completely released.
Note that in all cases the drug release is linear with $\sqrt{\tau}$ for a time of $\sqrt{\tau} \simeq 0.2$ after which each of the curves diverge. As regards the rate at which the drug is released over time, we find that the linear and exponential cases both release the drug linearly in $\sqrt{\tau}$ until about $\sqrt{\tau} \simeq 0.2$ after which there is a marked decrease in the rate at which the drug is released. It is clear that the case which represents the most continuous linear drug release rate for both the linear and exponential cases is the $r = 0$ case. In this case the rate of drug released remains constant, with $\sqrt{\tau}$, for the longest period. If, on the other hand, it is required that the drug be

released at a slower rate as the polymer swells the larger swell rates are the better choice. Similarly, if it is required that the amount of drug released remains constant for as long as possible these higher rates are the better choice, especially for the exponential case. A polymer which obeys these kind of swell rates is then required. On the other hand the logistic case possesses no such varied behaviour. In all cases of r the behaviour is similar with the drug being released at similar rates although lower as the polymer swells.

5 Time Dependent Diffusion Coefficient

Consider the diffusion coefficient as a function of domain expansion ratio $X(t)/L$

$$D = D\left(\frac{X(t)}{L}\right) = D(t)$$

since $X(t)$ is a function of t. Now the original PDE reads:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2} - \left(\frac{\dot{X}}{X}x\right)\frac{\partial c}{\partial x} - \left(\frac{\dot{X}}{X}\right)c \qquad \text{in } 0 < x < X(t),\ t > 0$$

$$\left.\begin{array}{ll} c(x,0) = 1 & 0 < x < X(0) \\ X(0) = L & \\ \frac{\partial c}{\partial x}(0,t) = 0 & \\ c(X(t),t) = 0 & \end{array}\right\} \quad \text{for } t > 0$$

Note that here D is a function of t only not x. Now define a new time variable [3] as

$$T = \int_0^t D(t')\,dt', \qquad \frac{dT}{dt} = D(t)$$

then the time derivatives may be transformed as

$$\frac{\partial c}{\partial t} = \frac{\partial c}{\partial T}\frac{dT}{dt} = D(t)\frac{\partial c}{\partial T}, \qquad \frac{dX}{dt} = D(t)\frac{dX}{dT}$$

so that we have:

$$\frac{\partial c}{\partial T} = \frac{\partial^2 c}{\partial x^2} - x\left(\frac{\dot{X}}{X}\right)\frac{\partial c}{\partial x} - \left(\frac{\dot{X}}{X}\right)c \qquad \text{in } 0 < x < X(T),\ T > 0$$

$$\left.\begin{array}{ll} c(x,0) = 1 & 0 < x < X(0) \\ X(0) = L & \\ \frac{\partial c}{\partial x}(0,T) = 0 & \\ c(X(T),T) = 0 & \end{array}\right\} \quad \text{for } T > 0$$

where $\dot{X} = dX/dT$. Now using the Landau transformation $\zeta = x/X(T)$, $\tau = T$, we have:

$$\frac{\partial c}{\partial \tau} = \frac{1}{X^2}\frac{\partial^2 c}{\partial \zeta^2} - \left(\frac{\dot{X}}{X}\right) c \qquad \text{in } 0 < \zeta < 1,\ \tau > 0 \tag{19}$$

$$\left.\begin{array}{l} c(\zeta, 0) = 1 \qquad 0 < \zeta < 1 \\ \\ \frac{\partial c}{\partial \zeta}(0, \tau) = 0 \\ c(1, \tau) = 0 \end{array}\right\} \quad \text{for } \tau > 0 \tag{20}$$

which may be solved for to get in terms of x and T:

$$c(x, T) = \frac{4}{\pi}\sum_{n=0}^{\infty} \frac{(-1)^n}{(2n+1)}\frac{L}{X(T)} \cos\left(\frac{(2n+1)\pi x}{2X(T)}\right) e^{-\left(\frac{(2n+1)\pi}{2}\right)^2 \int_0^T X^{-2}\, dt} \tag{21}$$

and for the fractional drug release as :

$$M(T) = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} e^{-\left(\frac{(2n+1)\pi}{2}\right)^2 \int_0^T X^{-2}\, dt} \tag{22}$$

5.1 Expansion of D for Small Times

The time dependent diffusion coefficient may be expanded in a Taylor series about $t = 0$ up to second order in time, see Appendix 6.6, and using the fact that $X(t) = Lf(t)$ with $f(0) = 1$

$$D(t) = \frac{1}{L^2}\left[D(1)t + \frac{\dot{f}(0)}{2}\left(D'(1) - 2D(1)^2\right)t^2\right]$$

so that for small time the fractional release reads:

$$M(t) = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} e^{-\left(\frac{(2n+1)\pi}{2L}\right)^2 \left[D(1)t + \frac{\dot{f}(0)}{2}\left(D'(1) - 2D(1)^2\right)t^2\right]}$$

this is approximated by:

$$M(t) \simeq \frac{2}{L}\sqrt{\frac{D(1)}{\pi}} t^{\frac{1}{2}} \left[1 + \frac{\dot{f}(0)}{4}\left(\frac{D'(1)}{D(1)} - 2D(1)\right)t\right]$$

which approximates the earlier obtained expression for small times when D is constant. Note that when $D'(1) = 0$, i.e. when the diffusion coefficient is not increasing with time, we have:

$$M(t) \simeq \frac{2}{L}\sqrt{\frac{D(1)}{\pi}} t^{1/2} \left[1 - \frac{1}{2}\dot{f}(0)D(1)t\right]$$

the above also shows that higher order terms are of relevance only when the domain is expanding, i.e. when $\dot{f} \neq 0$. Note also that this produces a release relationship of the form

$$M(t) \simeq k_1 t^{1/2} + k_2 t^{3/2} \tag{23}$$

where this is usually interpreted to imply a diffusion-controlled process $k_1 t^{1/2}$ and an advective (read relaxation)-controlled transport process [14]. Whereas the first term in (23) is a diffusion process, the second term is a combination of advection and diffusion and canot be directly related to empirical models which assume two separate contributions with the second being of the form kt. This cannot be expected in this model given that the second term has contributions both from diffusion and advection and that the model does not solve a Stefan problem where the moving front is obtained as part of the solution procedure. The present model assumes simple boundary growth and observes its consequences.

6 Appendix

6.1 The Landau Transformation

The Landau transformation is defined by

$$\zeta = \frac{x}{X(t)}, \qquad \tau = t$$

the diffusion equation (5) is transformed with the use of the new variables ζ and τ. The derivatives become:

$$\frac{\partial c}{\partial t} = \frac{\partial c}{\partial \zeta}\frac{\partial \zeta}{\partial t} + \frac{\partial c}{\partial \tau}\frac{\partial \tau}{\partial t} = -\frac{x}{X^2}\frac{\partial c}{\partial \zeta} + \frac{\partial c}{\partial \tau}$$

$$= -\zeta\frac{\dot{X}}{X}\frac{\partial c}{\partial \zeta} + \frac{\partial c}{\partial \tau}$$

similarly:

$$\frac{\partial c}{\partial x} = \frac{\partial c}{\partial \zeta}\frac{\partial \zeta}{\partial x} = \frac{1}{X}\frac{\partial c}{\partial \zeta}$$

so that:

$$\frac{\partial^2 c}{\partial x^2} = \frac{1}{X^2}\frac{\partial^2 c}{\partial \zeta^2}$$

The new domain is now given by:

$$x : 0 \to X(t), \qquad \zeta : 0 \to 1$$

and the new diffusion equation becomes:

$$-\zeta\frac{\dot{X}}{X}\frac{\partial c}{\partial \zeta} + \frac{\partial c}{\partial \tau} = \frac{D}{X^2}\frac{\partial^2 c}{\partial \zeta^2} - \zeta\frac{\dot{X}}{X}\frac{\partial c}{\partial \zeta} - \frac{\dot{X}}{X}c \qquad \text{in } 0 < \zeta < 1,\ \tau > 0$$

$$c(\zeta, 0) = 1 \qquad 0 < \zeta < 1$$

$$\left.\begin{array}{l} \frac{\partial c}{\partial \zeta}(0, t) = 0 \\ c(1, t) = 0 \end{array}\right\} \quad \text{for } \tau > 0$$

6.2 Analytic Solution for $c(\zeta, \tau)$ by Separation of Variables

This problem (7), (8) is solvable via a separation of variables as follows:

$$c(\zeta, t) = A(\zeta)B(\tau)$$

giving:

$$A\dot{B} = \frac{D}{X^2}A''B - \frac{\dot{X}}{X}AB$$

divide through by AB and rearrange to get all time dependent functions on the left and space dependent on the right:

$$\frac{X^2}{D}\frac{\dot{B}}{B} + \frac{\dot{X}X}{D} = \frac{A''}{A} = -\lambda^2$$

the two ordinary differential equations are:

$$\dot{B} + \left(\frac{\dot{X}}{X} + \frac{\lambda^2 D}{X^2}\right)B = 0$$

and

$$A'' + \lambda^2 A = 0$$

6.2.1 The Solution for $A(\zeta)$

The ODE above now reads:

$$A'' + \lambda^2 A = 0$$

subject to the boundary conditions:

$$A'(0) = 0, \qquad A(1) = 0$$

This may be solved in terms of sines and cosines:

$$A(\zeta) = a_1 \sin\lambda\zeta + a_2 \cos\lambda\zeta$$

applying the BCs we have:

$$A'(0) = \lambda(a_1 + 0) = 0, \Rightarrow a_1 = 0, \text{ for } \lambda \neq 0$$

therefore

$$A(\zeta) = a_2 \cos\lambda, \text{ so that } A(1) = a_2 \cos\lambda = 0$$

so $\lambda = (2n+1)\pi/2$ and the solution reads:

$$A(\zeta) = a_2 \cos\frac{(2n+1)\pi\zeta}{2}$$

6.2.2 The Solution for $B(\tau)$

We have:

$$\frac{dB}{d\tau} = -\left(\frac{\dot{X}}{X} + \frac{\lambda^2 D}{X^2}\right) B$$

giving:

$$\frac{1}{B}\, dB = -\left(\frac{\dot{X}}{X} + \frac{\lambda^2 D}{X^2}\right)\, d\tau$$

or

$$\ln B = -\int_0^\tau \frac{\dot{X}}{X} + \frac{\lambda^2 D}{X^2}\, dt + \ln C$$

$$= -\ln X(t)|_0^\tau - D\lambda^2 \int_0^\tau X^{-2}\, dt + \ln C$$

$$\ln\left(\frac{BX}{CL}\right) = -D\lambda^2 \int_0^\tau X^{-2}\, dt$$

using $X(0) = L$, so that:

$$B(\tau) = \frac{CL}{X(\tau)} e^{-D\lambda^2 \int_0^\tau X^{-2}\, dt}$$

6.2.3 The Full Solution

The final complete solution is expressed via a superposition as:

$$c(\zeta, \tau) = \sum_{n=0}^{\infty} C_n \frac{L}{X(\tau)} \cos\left(\frac{(2n+1)\pi\zeta}{2}\right) e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2 \int_0^\tau X^{-2}\, dt}$$

for some constants C_n. Now using the initial condition we have:

$$c(\zeta, 0) = \sum_{n=0}^{\infty} C_n \cos\left(\frac{(2n+1)\pi\zeta}{2}\right) = 1 \tag{24}$$

6.2.4 The Orthogonality Integral

Remembering the orthogonality properties of cosines:

$$\int_0^1 \cos\left(\frac{(2n+1)\pi\zeta}{2}\right) \cos\left(\frac{(2m+1)\pi\zeta}{2}\right) d\zeta = \begin{cases} 0 & \text{if } n \neq m \\ 1/2 & \text{if } n = m \neq 0 \\ 1 & \text{if } n = m = 0 \end{cases}$$

for integers n, m. Then integrating both sides after multiplying (24) by $\cos\left(\frac{(2m+1)\pi\zeta}{2}\right)$, we have:

$$\int_0^1 \cos\left(\frac{(2m+1)\pi\zeta}{2}\right)\, d\zeta = \sum_{n=0}^{\infty} C_n \int_0^1 \cos\left(\frac{(2n+1)\pi\zeta}{2}\right) \cos\left(\frac{(2m+1)\pi\zeta}{2}\right)\, d\zeta$$

$$= C_m/2$$

therefore:

$$C_m = 2\int_0^1 \cos\left(\frac{(2m+1)\pi\zeta}{2}\right)\, d\zeta = \frac{4}{(2m+1)\pi}\left[\sin\left(\frac{(2m+1)\pi\zeta}{2}\right)\right]_{\zeta=0}^{\zeta=1}$$

so that

$$C_m = \frac{4(-1)^m}{(2m+1)\pi}$$

The solution reads:

$$c(\zeta,\tau) = \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{(-1)^n}{(2n+1)}\frac{L}{X(\tau)}\cos\left(\frac{(2n+1)\pi\zeta}{2}\right)e^{-D\left(\frac{(2n+1)\pi}{2}\right)^2\int_0^\tau X^{-2}\,dt} \tag{25}$$

6.3 Fractional Drug Release ODE

We may make use of the original PDE (7) and the boundary and initial conditions (8) to construct an ODE for the fractional drug release over time $M(\tau)$. The definition of $M(\tau)$ implies that:

$$\int_0^1 c(\zeta,\tau)\, d\zeta = (1 - M(\tau))\frac{L}{X}$$

in addition the initial condition implies:

$$\int_0^1 c(\zeta,0)\, d\zeta = 1 = (1 - M(0))\frac{L}{X(0)} \Rightarrow M(0) = 0$$

therefore take the space integral between zero and one for the PDE (7), we get:

$$\frac{\partial}{\partial\tau}\int_0^1 c(\zeta,\tau)\, d\zeta = \frac{D}{X^2}\int_0^1 \frac{\partial^2 c}{\partial\zeta^2}\, d\zeta - \frac{\dot{X}}{X}\int_0^1 c(\zeta,\tau)\, d\zeta$$

or

$$\frac{d}{d\tau}(1 - M(\tau))\frac{L}{X} + \frac{\dot{X}}{X}(1 - M(\tau))\frac{L}{X} = \frac{D}{X^2}\left[\frac{\partial c(1,\tau)}{\partial\zeta} - \frac{\partial c(0,\tau)}{\partial\zeta}\right]$$

giving:

$$-\frac{L}{X}\frac{dM(\tau)}{d\tau} - \frac{L\dot{X}}{X^2}(1 - M(\tau)) + \frac{L\dot{X}}{X^2}(1 - M(\tau)) = \frac{D}{X^2}c_\zeta(1,\tau)$$

therefore:

$$\frac{dM(\tau)}{d\tau} = -\frac{D}{LX}c_\zeta(1,\tau)$$

so that:

$$M(\tau) = -\frac{D}{L}\int_0^\tau \frac{c_\zeta(1,t)}{X(t)}\, dt \equiv -\frac{D}{L^2}\int_0^\tau \frac{c_\zeta(1,t)}{f(t)}\, dt$$

6.4 Variation with Half-Life

6.4.1 The Static Case

Note that the expression for the fractional drug release over time for the static case reads:

$$M_S(\tau) = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2}\, e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2\tau}$$

$$= 1 - \frac{8}{\pi^2}\left[e^{-\left(\frac{\pi\sqrt{D\tau}}{2L}\right)^2} + \frac{1}{9}e^{-\left(\frac{3\pi\sqrt{D\tau}}{2L}\right)^2} + \frac{1}{25}e^{-\left(\frac{5\pi\sqrt{D\tau}}{2L}\right)^2} + ...\right]$$

for small time the first of these terms remains the largest so that:

$$M_S(\tau) \simeq 1 - \frac{8}{\pi^2}e^{-D\left(\frac{\pi}{2L}\right)^2\tau}$$

note that the fractional drug release reaches its half way point for a time τ_{hf} given by:

$$\frac{1}{2} = 1 - \frac{8}{\pi^2}e^{-D\left(\frac{\pi}{2L}\right)^2\tau_{hf}}$$

so that

$$\tau_{hf} = -\frac{4L^2}{\pi^2 D}\ln\left(\frac{\pi}{4}\right)^2 \tag{26}$$

which for $D = L = 1$ gives $\tau_{hf} \simeq 0.2$, which if taken on the $\tau^{1/2}$ coordinate line gives $\sqrt{\tau_{hf}} \simeq 0.44$. This coincides quite well with the estimated deviation time of the relative difference between the analytical and small time solutions.

6.4.2 Linear Growth

A similar calculation shows that for the linear dynamic case, equation (14):

$$\tau_{hf} = \frac{-\frac{1}{D}\left(\frac{2L}{\pi}\right)^2\ln\left(\frac{\pi}{4}\right)^2}{1 + \frac{r}{D}\left(\frac{2L}{\pi}\right)^2\ln\left(\frac{\pi}{4}\right)^2}$$

which coincides with the static case when $r = 0$. This is valid provided $r \neq -D(\pi/2L)^2/\ln(\pi/4)^2$.

6.4.3 Exponential Growth

Again, the same calculation for the exponential dynamic case, equation (16), obtains:

$$\tau_{hf} = -\frac{1}{2r}\ln\left(1 + \frac{2r}{D}\left(\frac{2L}{\pi}\right)^2\ln\left(\frac{\pi}{4}\right)^2\right)$$

for $r \neq 0$ and in fact $r > -(D/2)(\pi/2L)^2/\ln(\pi/4)^2$.

	static		linear		exponential	
r	t_{hf}	$\sqrt{t_{hf}}$	t_{hf}	$\sqrt{t_{hf}}$	t_{hf}	$\sqrt{t_{hf}}$
0	0.20	0.44	0.20	0.44	NA	NA
1	NA	NA	0.25	0.50	0.25	0.50
2	NA	NA	0.33	0.57	0.38	0.62
3	NA	NA	0.50	0.70	NA	NA
4	NA	NA	1.00	1.00	NA	NA

Table 2: Table showing the time required for half of the drug to be released for the static and dynamic cases using $L = D = 1$. Here, NA means Not Applicable.

6.4.4 Logistic Growth

For the logistic case an exact expression for the half-life cannot be obtained given the mix of time terms involved in equation (18).

The half-lives for the static, linear and exponential cases, for $L = D = 1$, are shown in Table 2. These results match well the times which can be read off the graphs of Figure 9.

6.5 Fractional Drug Release for General X at Small Times

We have:

$$M(\tau) = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 I}$$

for

$$I(\tau) = \int_0^\tau f(t)^{-2}\, dt$$

now, assume that f may be expanded in a Taylor series about $t = 0$ as:

$$f(t) \simeq f(0) + f'(0)t + \frac{f''(0)t^2}{2!} + O(t^3)$$

then up to first order we have:

$$I(\tau) = \int_0^\tau f(t)^{-2}\, dt \simeq \int_0^\tau [f(0) + f'(0)t]^{-2}\, dt$$

$$= \frac{1}{[f(0)]^2} \int_0^\tau \left[1 + \frac{f'(0)}{f(0)}t\right]^{-2} dt$$

$$\simeq \frac{1}{[f(0)]^2} \int_0^\tau 1 - 2\frac{f'(0)}{f(0)}t\, dt$$

$$= \frac{\tau}{[f(0)]^2} - \frac{f'(0)}{[f(0)]^3}\tau^2$$

Now since for any function representing the growing boundary $f(0) = 1$. Therefore for any such function at small times it 'looks' like the static case:

$$M(\tau) \simeq 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 \tau}$$

for small times which implies that

$$M(\tau) = \frac{2}{L}\sqrt{\frac{D}{\pi}}\tau^{1/2}$$

for any kind of dynamic boundary with $f(\tau) \geq 1$ for $\tau \geq 0$.

6.6 Taylor Series Expansion of $D(t)$

$$D\left(\frac{X(t)}{L}\right) = D\left(\frac{X(0)}{L}\right) + \left.\frac{dD}{dt}\right|_{t=0} t + ...$$

but since at $X(0) = L$:

$$\frac{dD}{dt} = \frac{dD}{d(X/L)}\frac{d(X/L)}{dt} = \frac{D'(X/L)\dot{X}(t)}{L}$$

then

$$D(X(t)/L) = D(1) + \left(\frac{D'(1)\dot{X}(0)}{L}\right) t + ...$$

then the integral up to second order in time is

$$T = \int_0^t D(X(t')/L)\, dt' \simeq \int_0^t D(1) + \left(\frac{D'(1)\dot{X}(0)}{L}\right) t'\, dt'$$

$$= D(1)t + \left(\frac{D'(1)\dot{X}(0)}{2L}\right) t^2$$

similarly the integral

$$\int_0^T X(t)^{-2}\, dt \simeq \frac{1}{X(0)^2}\left(T - \frac{\dot{X}(0)}{X(0)}T^2\right)$$

substituting for T

$$\int_0^T X(t)^{-2}\, dt = \frac{1}{X(0)^2}\left[D(1)t + \left(\frac{D'(1)\dot{X}(0)}{2L}\right) t^2 - \frac{\dot{X}(0)}{X(0)}\left(D(1)t + \left(\frac{D'(1)\dot{X}(0)}{2L}\right) t^2\right)^2\right]$$

6.7 Sum to n Terms of $M(\tau)$

Given the general solution to fractional drug release:

$$M(\tau) = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 I}$$

where $I(\tau) = \int_0^\tau f(t)^{-2}\, dt$. Then the sum becomes:

$$M(\tau) = 1 - \frac{8}{\pi^2} e^{-D\left(\frac{\pi}{2L}\right)^2 I} - \sum_{n=1}^{\infty} \frac{8}{(2n+1)^2\pi^2} e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 I}$$

the second sum may be summed to n terms with use of the integral test of Calculus, that is, the convergence and the sum to n terms may be expressed through the integral:

$$\frac{8}{\pi^2} \int_n^\infty \frac{e^{-D\left(\frac{(2x+1)\pi}{2L}\right)^2 I}}{(2x+1)^2}\, dx$$

now let $y = \sqrt{DI}(2x+1)\pi/2L$, $dy = \sqrt{DI}\pi dx/L$, $x : n \to \infty$, $y : \sqrt{DI}(2n+1)\pi/2L \to \infty$. We have:

$$\frac{2\sqrt{DI}}{\pi L} \int_{\frac{(2n+1)\sqrt{DI}\pi}{2L}}^\infty \frac{e^{-y^2}}{y^2}\, dy$$

the integral may be solved by integration by parts by setting:

$$u = e^{-y^2}, du = -2ye^{-y^2}\, dy; \quad dv = y^{-2}dy \Rightarrow v = -y^{-1}$$

or:

$$\int_{\frac{(2n+1)\sqrt{DI}\pi}{2L}}^\infty \frac{e^{-y^2}}{y^2}\, dy = -\left.\frac{e^{-y^2}}{y}\right|_{\frac{(2n+1)\sqrt{DI}\pi}{2L}}^\infty - \int_{\frac{(2n+1)\sqrt{DI}\pi}{2L}}^\infty \frac{2ye^{-y^2}}{y}\, dy$$

$$= \frac{2Le^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 I}}{\sqrt{DI}(2n+1)\pi} - 2\int_{\frac{(2n+1)\sqrt{DI}\pi}{2L}}^\infty e^{-y^2}\, dy$$

the integral on the right is an error function [3], i.e.

$$\frac{2}{\sqrt{\pi}} \int_z^\infty e^{-x^2}\, dx = \text{erfc } z$$

in fact we get:

$$= \frac{2Le^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 I}}{\sqrt{DI}(2n+1)\pi} - \sqrt{\pi}\text{erfc}\left(\frac{(2n+1)\sqrt{DI}\pi}{2L}\right)$$

the final solution is then:

$$\frac{2\sqrt{DI}}{\pi L}\int_{\frac{(2n+1)\sqrt{DI}\pi}{2L}}^{\infty}\frac{e^{-y^2}}{y^2}\,dy=\frac{4e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 I}}{(2n+1)\pi^2}-\frac{2}{L}\sqrt{\frac{DI}{\pi}}\mathrm{erfc}\left(\frac{(2n+1)\sqrt{DI}\pi}{2L}\right)$$

therefore the sum up to n terms ($n=1,2,3,...$) of $M(\tau)$ is:

$$M(\tau)=1-\frac{8}{\pi^2}e^{-D\left(\frac{\pi}{2L}\right)^2 I}-\frac{4e^{-D\left(\frac{(2n+1)\pi}{2L}\right)^2 I}}{(2n+1)\pi^2}+\frac{2}{L}\sqrt{\frac{DI}{\pi}}\mathrm{erfc}\left(\frac{(2n+1)\sqrt{DI}\pi}{2L}\right) \quad (27)$$

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